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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,729	11/17/2003	Jean-Pierre Sommadossi	11874-064-999 (IDX 1022)	5135

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	

ART UNIT	PAPER NUMBER
1648	

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12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,729	SOMMADOSSI ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34,38-40,87,89,92,101,103-107 and 109-122* is/are pending in the application.

4a) Of the above claim(s) *38 and 87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,39,40,89,92,101,103-107 and 109-122* is/are rejected.

7)☒ Claim(s) *107* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 September 2008 has been entered.

DETAILED ACTION

This Office Action is in response to the amendment filed 26 September 2008. Claims 1-32, 35-37, 41-86, 88, 90, 91, 93-100, 102, and 108 have been cancelled. Claims 109-122 have been added. Claims 33, 34, 38-40, 87, 89, 92, 101, 103-107 and 109-122 are pending. Claims 38 and 87 are withdrawn. Claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 are currently examined.

Claim Objections

Claim 107 is objected to because of a grammatical error in the phrase "the method of any one of claim 33." Applicants may consider deleting the phrase "any one of" from the claim language. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15 and 16 of U.S. Patent No. 7,169,766B2 in view of Arens *et al.* (2001).

The instant claims are drawn to a method for treating a hepatitis C virus infection in a host, comprising (a) administering an effective amount of a 2'-branched nucleoside or a pharmaceutically acceptable prodrug or salt thereof to the host; (b) identifying viral resistance to the 2'-branched nucleoside in the host; and (c) administering to the host, who is infected with the virus resistant to the 2'- branched nucleoside, an effective amount of one or more drugs that directly or indirectly induce a mutation in a hepatitis C virus at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence,

XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region. Such a drug is more specifically limited to interferon.

The patented claims are drawn to a method for the treatment of a hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a beta-D-2'-branched nucleoside compound or a pharmaceutically acceptable salt or ester thereof in combination or alternation with a second agent, especially an interferon.

The patent claims differ from the instant claims in that they do not recite the step of identifying viral resistance to the 2'-branched nucleoside in the host.

Arens *et al.* discloses that HCV can be treated by the combination of interferon and ribavirin but certain strains of virus are more resistant to treatment than others and suggests that genotyping of HBV, HCV, CMV, and HIV is important to the therapeutic regimen (Abstract). Specifically for HBV, Arens suggests drug susceptibility testing comprising a genotype assay detecting mutations in the genome that may confer drug resistance and a phenotypic assay measuring replication fitness, which is the actual ability of the virus to grow in the presence of various chemical compounds or known antiviral drugs (page 12, right column). As a general genotyping approach for all of the viruses but as an example for genotyping/phenotyping CMV, DNA is extracted from whole blood (page 21, right column, second paragraph) and the phenotypic analysis is done by plaque reduction assay (page 21, right column, first paragraph). More specifically, Arens suggests different genotyping methods including sequencing, primer-specific PCR and hybridization that can detect mutations at certain locations within a specific genome (page 13, left column, first paragraph).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the HCV treatment method in the claims of US Patent No. 7,169,766 B2 so as to add the step of identifying viral resistance to the 2'-branched nucleoside in the host with a reasonable expectation of success because Arens suggests that the determination of HCV genotype and evaluating the viral phenotype is important to the regimen. One having ordinary skill in the art would have been motivated to modify the Carroll method to determine the efficacy of the 2'-branched nucleoside and to identify the clinical outcome associated with the interferon alone or the combination of the 2'-branched nucleoside with interferon, as per the teachings of Arens *et al.*

Claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-7, 9, 12, 13 and 17 of U.S. Patent No. 7,192,936B2 in view of Arens *et al.* (2001).

The instant claims are drawn to a method for treating hepatitis C virus infection in a host, comprising (a) administering an effective amount of a 2'-branched nucleoside or a pharmaceutically acceptable prodrug or salt thereof to the host; (b) identifying viral resistance to the 2'-branched nucleoside in the host; and (c) administering to the host, who is infected with the virus resistant to the 2'- branched nucleoside, an effective amount of one or more drugs that directly or indirectly induce a mutation in a hepatitis C virus at a location other than a mutation of a nucleotide that results in a change from

serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region. Such a drug is more specifically limited to interferon.

The patented claims are drawn to a method for the treatment of a Flaviviridae virus infection, specifically limited to a hepatitis C virus infection, in a host, comprising administering an anti-virally effective amount of a -2'-branched nucleoside compound or a pharmaceutically acceptable salt or ester thereof in combination or alternation with a second agent, especially an interferon.

The patent claims differ from the instant claims in that they do not recite the step of identifying viral resistance to the 2'-branched nucleoside in the host.

Arens *et al.* discloses that HCV can be treated by the combination of interferon and ribavirin but certain strains of virus are more resistant to treatment than others and suggests that genotyping of HBV, HCV, CMV, and HIV is important to the therapeutic regimen (Abstract). Specifically for HBV, Arens suggests drug susceptibility testing comprising a genotype assay detecting mutations in the genome that may confer drug resistance and a phenotypic assay measuring replication fitness, which is the actual ability of the virus to grow in the presence of various chemical compounds or known antiviral drugs (page 12, right column). As a general genotyping approach for all of the viruses but as an example for genotyping/phenotyping CMV, DNA is extracted from whole blood (page 21, right column, second paragraph) and the phenotypic analysis is done by plaque reduction assay (page 21, right column, first paragraph). More specifically, Arens suggests different genotyping methods including sequencing, primer-

specific PCR and hybridization that can detect mutations at certain locations within a specific genome (page 13, left column, first paragraph).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the HCV treatment method in the claims of US Patent No. 7,169,766 B2 so as to add the step of identifying viral resistance to the 2'-branched nucleoside in the host with a reasonable expectation of success because Arens suggests that the determination of HCV genotype and evaluating the viral phenotype is important to the regimen. One having ordinary skill in the art would have been motivated to modify the Carroll method to determine the efficacy of the 2'-branched nucleoside and to identify the clinical outcome associated with the interferon alone or the combination of the 2'-branched nucleoside with interferon, as per the teachings of Arens *et al.*

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> The changes made to 35 U.S.C. §102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. §102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. §102(e)).

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of claims 33, 34, 92, 104 and 107 under 35 U.S.C. §102(e) as being anticipated by Carroll *et al.* (US 7,105,499 B2) is **withdrawn** in response to Applicant's amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 39, 40, 89, 101, 103, 105 and 106 under 35 U.S.C. §103(a) as being obvious over Carroll *et al.* (US 7,105,499 B2) in view of Sinko *et al.* (1998) is **withdrawn** in response to Applicants' amendment.

New Grounds of Rejection

Claims 33, 34, 92, 104, 107 and 109-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carroll *et al.* (US 7,105,499 B2, priority filing date 22 January 2001, hereinafter "Carroll") in view of Arens *et al.* (2001, hereinafter "Arens").

The instant claims are drawn to a method for treating a hepatitis C virus infection in a host, comprising (a) administering an effective amount of a 2'-branched nucleoside

or a pharmaceutically acceptable prodrug or salt thereof to the host; (b) identifying viral resistance to the 2'-branched nucleoside in the host; and (c) administering to the host, who is infected with the virus resistant to the 2'- branched nucleoside, an effective amount of one or more drugs that directly or indirectly induce a mutation in a hepatitis C virus at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region.

Carroll discloses a method of treating RNA-dependent RNA viral infection or an HCV infection, by administering a compound such as 2'-methyl-cytidine (column 15, line 14-67), in combination or alternation with other agents like ribavirin, viramidine, levovirin, thymosin alpha-1, HCV NS3 serine protease inhibitor, interferon-a-2b (column 32), VX-497, mycophenolate mofetil, amantadine and 2'-C-branched ribonucleosides (column 33), in association with a pharmaceutically acceptable carrier (column 2, lines 54-57). The HCV NS3 serine protease inhibitor and interferon are drugs that directly or indirectly induce a mutation in a HCV at a location other than the serine in the XRXSGXXXT sequence of RNA polymerase B region.

Carroll does not disclose step (b) of identifying viral resistance.

Arens *et al.* discloses that HCV can be treated by the combination of interferon and ribavirin but certain strains of virus are more resistant to treatment than others and suggests that genotyping of HBV, HCV, CMV, and HIV is important to the therapeutic regimen (Abstract). Specifically for HBV, Arens suggests drug susceptibility testing comprising a genotype assay detecting mutations in the genome that may confer drug

resistance and a phenotypic assay measuring replication fitness, which is the actual ability of the virus to grow in the presence of various chemical compounds or known antiviral drugs (page 12, right column). As a general genotyping approach for all of the viruses but as an example for genotyping/phenotyping CMV, DNA is extracted from whole blood (page 21, right column, second paragraph) and the phenotypic analysis is done by plaque reduction assay (page 21, right column, first paragraph). More specifically, Arens suggests different genotyping methods including sequencing, primer-specific PCR and hybridization that can detect mutations at certain locations within a specific genome (page 13, left column, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Carroll method so as to add the step of identifying viral resistance to the 2'-branched nucleoside in the host with a reasonable expectation of success because Arens suggests that the determination of HCV genotype and evaluating the viral phenotype is important to the regimen. One would be motivated to modify the Carroll method to determine the efficacy of the 2'-branched nucleoside and to identify the clinical outcome associated with the interferon alone or the combination of the 2'-branched nucleoside with interferon. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carroll *et al.* (US 7,105,499 B2, priority filing

date 22 January 2001, hereinafter "Carroll") in view of Arens *et al.* (2001, hereinafter "Arens") and Sinko *et al.* (1998, hereinafter "Sinko").

The instant invention is further limited to a valinyl ester prodrug of the 2'-branched pyrimidine.

The relevance of Carroll and Arens is set forth above. Carroll and Arens do not disclose an amino acid ester prodrug.

Sinko discloses valacyclovir (VACV), the L-valyl ester of the acyclic nucleoside analog of deoxyguanosine. Sinko suggests that L-valyl ester prodrug demonstrates an oral availability that is 3-5 times greater than acyclovir, concentration dependent, and saturable in humans (Abstract). Sinko further discloses that the mean absolute oral bioavailability of VACV is three to five times that of acyclovir in humans. See page 209, right column, second paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Carroll method so as to replace the 3'-OH group of 2'-branched nucleoside with a valine ester group to make a valinyl ester prodrug with a reasonable expectation of success because Sinko teaches that a valinyl ester prodrug can enhance the oral bioavailability of the nucleoside drug and improve the intestinal uptake of nucleoside analog acyclovir. One would be motivated to improve the oral availability of the 2'-branched nucleoside by making it more saturable in humans as suggested by Sinko. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648
16 December 2008
/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648